Adenocarcinoma of the Esophagus: Risk Factors and Prevention

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Esophageal cancer, with an estimated number of 12,300 new cases in the year 2000, is relatively uncommon in the United States but produces a high number of annual deaths, estimated at 12,100. Moreover, the incidence of the

Introduction

The estimated number of new cases of esophageal cancer (adenocarcinoma and squamous cell carcinoma) in the United States is 12,300, and, unfortunately, the estimated number of deaths from this cancer is 12,100.[1] Of the 12,300 new cases, 9,300 occur in males—a reflection of the fact that this disease is three times more likely to occur in males than females.

The incidence of adenocarcinoma of the esophagus has risen dramatically in the past two decades in the United States, Great Britain, and Scandinavia.[2] In white males under 65 years of age, the rate of adenocarcinoma has doubled, whereas in white males over the age of 65 years, there has been a three- to fourfold increase in age-adjusted incidence rates.[3] Although the overall incidence of squamous cell carcinoma of the esophagus is declining, this histologic type remains six times more likely to occur in African-American males than in white males (Figure 1).[3,4]

These disturbing changes in esophageal cancer epidemiology have driven researchers to study possible risk factors. Identification of risk factors could lead to primary prevention, as well as earlier diagnosis, treatment and increased survival.

Risk Factors

Various risk factors for the development of esophageal adenocarcinoma have been identified (Table 1). These include Barrett’s esophagus, acid peptic disorders, motor disorders of the esophagus, other malignancies, medications, environmental exposures, diet, and nutrition.

Barrett’s Esophagus

Barrett’s esophagus is a disease that occurs when metaplastic columnar epithelium replaces normal stratified squamous epithelium of the distal esophagus.[5] The number of Americans with Barrett’s esophagus is estimated to be 700,000, but the true prevalence is most likely higher because of asymptomatic, undiagnosed disease.

Barrett’s esophagus is attributed primarily to chronic gastroesophageal reflux disease (GERD).[6,7] The chronic acidic environment damages the squamous epithelial lining, and, subsequently, undifferentiated pluripotent stem cells (either already present or newly migrated to the area) develop into columnar epithelium. Other mechanisms, including tobacco-and alcohol-associated damage to the esophageal epithelium, may also contribute to the development of Barrett’s esophagus, but overall, GERD is believed to be the most prominent etiologic factor.

Different grades of dysplastic tissue (low-, indefinite-, or high-grade) can develop within Barrett’s esophagus. The progression from dysplasia to adenocarcinoma occurs when neoplastic cells break through the basement membrane. The risk of progression to esophageal adenocarcinoma in patients with Barrett’s esophagus is estimated to be 30- to 125-fold higher than that in the general population.[8,9] However, no precise odds ratio has been defined. Studies in the literature, however, report no difference in the actuarial survival of patients with Barrett’s esophagus (age greater than 55 years) compared to control populations.[8,10]

Calculating the cancer risk in patients with Barrett’s esophagus is difficult for a number of reasons. Only 10% to 12% of patients with symptomatic GERD who undergo endoscopy are found to have Barrett’s esophagus,[9] and, as mentioned above, the estimated number of people with asymptomatic Barrett’s esophagus is much higher than the number with symptomatic disease.[11] Autopsy studies examining for Barrett’s esophagus reveal a prevalence rate of 376 cases per 100,000 population.
Thus, for every 1 patient diagnosed, approximately 20 cases go undiagnosed.[12] Moreover, the number and quality of tissue biopsy specimens obtained during upper endoscopy and the accuracy of pathologic diagnosis are operator dependent and variable. Despite these limitations, patients with Barrett’s esophagus are recognized to have a higher risk for developing adenocarcinoma of the esophagus than the general population.

**Acid Peptic Disorders**

Gastroesophageal reflux occurs when the lower esophageal sphincter (LES) pressure is decreased and the gastrointestinal contents flow back into the esophagus. The complex pathophysiology of GERD results in damage to the esophageal epithelium and such clinical symptoms as heartburn, chest pain, and dysphagia. In addition to its role in the pathogenesis of Barrett’s esophagus, GERD is an independent risk factor for the development of adenocarcinoma. Lagergren et al found that recurrent symptoms of reflux were associated with a 7.7-fold (95% confidence interval [CI], 5.3 to 11.4) increase in the risk of esophageal adenocarcinoma but no increase in the risk of squamous cell carcinoma of the esophagus.[13]

Treatment of GERD involves conservative measures, such as sleeping with the head of the bed elevated, weight reduction, and smoking cessation, as well as medical therapy with histamine-2-receptor antagonists (H2 -blockers), proton pump inhibitors, and pro-kinetic agents. The objectives of non-medical and medical therapy are to reduce gastric pressure and increase LES pressure. Whether or not treatment of GERD decreases the risk of adenocarcinoma of the esophagus has yet to be determined.

**Complications of GERD**

One complication of GERD is esophagitis. The spectrum of esophagitis ranges from mild disease with no visible endoscopic damage to severe disease, characterized by erythema, bleeding, and inflammation, with granulocytes and eosinophils infiltrating the epithelium. Esophagitis alone as a consequence of GERD does not increase the risk of adenocarcinoma unless there is replacement of the squamous epithelium with columnar epithelium (Barrett’s esophagus). A hiatal hernia develops when a portion of the stomach protrudes through the diaphragm into the thoracic cavity. Hiatal hernia may play a role in the pathogenesis of GERD but, by itself, is not a risk factor for esophageal adenocarcinoma.

Gastric and/or duodenal ulcers also do not carry an increased risk of esophageal adenocarcinoma.

**Motor Disorders of the Esophagus**

**Achalasia** is a motor disorder involving the smooth muscle of the esophagus. The LES does not relax upon swallowing, and, as a result, abnormal contractions replace normal peristalsis. The esophagus progressively dilates as it fills up with food debris. Long-standing achalasia has been associated with squamous cell carcinoma of the esophagus. A population-based study conducted in Sweden by Sandler et al demonstrated that patients with achalasia are at increased risk of developing squamous cell cancer of the esophagus.[14] Similar findings were reported by Loviscek et al from Argentina based on their study of patients who had had achalasia and marked food retention for more than 20 years.[15] No studies have identified achalasia as a risk factor for esophageal adenocarcinoma.

**Scleroderma** (systemic sclerosis) is a disease that causes fibrosis of the skin, gastrointestinal tract, and other vital organs. Increased collagen deposits in the lower two-thirds of the esophagus and thinned mucosa result in a dysfunctional LES, the development of GERD, and, potentially, Barrett’s esophagus. Thus, the increased risk of esophageal adenocarcinoma is secondary to the development of Barrett’s esophagus.[16-18] Individuals with scleroderma and symptomatic GERD should be evaluated with upper endoscopy to look for the presence of early metaplastic or dysplastic changes.

**Other Malignancies**

**Colon Cancer**—Kingston et al reported that patients with colon cancer may be at an increased risk of developing esophageal adenocarcinoma.[19] Conversely, other studies have found that patients with Barrett’s esophagus have an increased prevalence of colon cancer.[20-22]

A case-control, population-based study conducted by Vaughan et al showed that men with adenocarcinoma of the colon were more likely to be diagnosed with esophageal adenocarcinoma than with squamous cell cancer of the esophagus.[23] Ahsan et al, in a retrospective cohort analysis, reported a similar small increase in relative risk for developing esophageal adenocarcinoma (1.44; 95% CI, 1.03 to 2.02) among men with colon cancer.[24] Both investigators found no association between the two cancers in women.

**Breast Cancer**—Small case series have reported an increased risk of esophageal cancer among women who received radiation therapy as part of their treatment for breast cancer. Ahsan et al performed a population-based, retrospective cohort study to evaluate this association.[25] He found...
that 10 or more years after receiving radiation therapy for breast cancer, women had a relative risk of 5.42 (95% CI, 2.33 to 10.68) for developing squamous cell cancer of the esophagus and a 4.22 risk (95% CI, 0.47 to 15.25) for developing esophageal adenocarcinoma. However, the confidence intervals for the effect estimate for the relative risk of adenocarcinoma did not exclude 0, perhaps due to the small number of patients in this cohort. There was no increased risk of esophageal cancer in women who did not receive radiotherapy for breast cancer.

**Prostate Cancer**
Lagergren et al performed a population-based retrospective cohort study in men with prostate cancer in Sweden to determine whether sex hormones (antiandrogenic treatment with estrogen) were the reason for the male predominance of esophageal adenocarcinoma.[26] They found no increase in relative risk in this population.

**Medications**
Medications that reduce LES pressure and increase GERD have been evaluated as potential risk factors for the development of esophageal adenocarcinoma. The drugs studied include calcium channel blockers, tricyclic antidepressants, theophylline, beta-agonists, and H2-blockers. No increase in risk has been found in several studies of calcium channel blockers.[27-29]

**Asthma Drugs**
An increased risk has been reported for individuals using theophylline (adjusted odds ratio, 2.5) or beta-agonists (adjusted odds ratio, 1.7) for asthma.[27] With long-term use (> 5 years), the adjusted odds ratios for the two drugs were higher, at 3.1 (95% CI, 0.9 to 10.3) and 2.3 (95% CI, 0.8 to 7.0), respectively.

**H2-blockers**
Theoretically, use of H2-blockers could increase the risk of esophageal cancer because the alkalinized duodenal contents damage the esophageal epithelium. Indeed, alkaline reflux is postulated to be a cause of Barrett’s esophagus.[30] Another possible mechanism is that use of H2-blockers may increase the number of nitrate-reducing bacteria colonizing the stomach and thereby increase levels of carcinogenic nitrosamines. However, these hypotheses are presently unsubstantiated.

Chow et al evaluated the role of H2-blockers and anticholinergics and reported that taking these agents poses no increased risk of developing esophageal adenocarcinoma.[31]

**Environmental Factors**
The risk for developing adenocarcinoma of the esophagus posed by occupational exposures to such agents as asbestos, silica, dusts, and metal-working fluids in the automotive industry, as well as rubber in tire production, remains unclear. Several studies demonstrate that individuals working in these industries are at increased risk of developing esophageal cancer, but the histologic type is not specified.[32-35]

**Tobacco**
Tobacco smoke is a clear environmental risk factor for the development of esophageal cancer. Zhang et al performed a hospital-based, case-control study in 596 patients in New York.[36] The odds ratio for developing esophageal adenocarcinoma were 1.46 (95% CI, 0.72 to 2.96) among smokers, compared to nonsmokers, and 2.36 (95% CI, 0.71-7.92) in patients whose smoking history was greater than 60 pack-years. In contrast, the odds ratios for developing squamous cell cancer of the esophagus in white and black males with greater than a 40-pack-year history of cigarette smoking were 5.9 (95% CI, 2.1 to 16.3) and 5.1 (95% CI, 2.3 to 11.6), respectively.[37]

Another study reported similar findings. The odds ratio for developing esophageal adenocarcinoma in smokers with a 40- to 79-pack-year history: was 2.4 (95% CI, 1.4 to 4.1), as compared with an odds ratio of 7.9 (95% CI, 2.8 to 22.1) for developing squamous cell cancer of the esophagus.[38] The risk of adenocarcinoma developing in former smokers remains elevated for up to 30 years from the time of smoking cessation, with an odds-ratio of 2.0 (95% CI, 1.4 to 2.9).[39] One possible explanation is that tobacco carcinogens act at an early stage of esophageal tumorigenesis. The pattern of smoking prevalence during the 20th century (increasing up to the 1970s) and histologic differences in risk reduction after cessation could provide one explanation for the epidemiologic changes observed for esophageal cancer.

Squamous cell cancer of the esophagus may be decreasing as a result of recent declines in tobacco use, while esophageal adenocarcinoma is still increasing in older males. Nonetheless, the risk of developing both types of esophageal cancer is higher in tobacco users than nonusers, and tobacco use remains a significant preventable risk factor.

**Alcohol**
Alcohol consumption is a clear risk factor for squamous cell carcinoma of the esophagus but may not increase the risk of adenocarcinoma. An odds ratio of only 1.8 (95% CI, 1.1 to 3.1) in patients with esophageal adenocarcinoma who consumed more than 21 drinks per week contrasts with an odds ratio of 9.5 (95% CI, 4.0 to 22.3) in patients with squamous cell cancer of the esophagus.[40]
odds ratio for adenocarcinoma was 2.6. (95% CI, 1.4 to 4.6) in patients who drank hard liquor, as compared with 1.0 (95% CI, 0.5 to 2.0) in patients who drank wine and beer. Interestingly, the odds ratio increased in patients who had stopped drinking for 15 years. In contrast, a study by Gammon et al reported no association of adenocarcinoma with liquor and beer and possibly an inverse association with wine consumption (odds ratio, 0.6; 95% CI, 0.5 to 0.8).[39] Users of both tobacco and alcohol did not have a higher odds ratio for developing esophageal adenocarcinoma when compared to users of tobacco alone. Thus, the contribution of alcohol to the rising trend in esophageal adenocarcinoma incidence is most likely minimal.

### Diet and Nutrition

#### Squamous Cell Carcinoma

Multiple epidemiologic studies in endemic areas, such as Japan and China, have evaluated various dietary risk factors. The majority of such studies have focused on squamous cell cancer of the esophagus, which is the prevalent histology in these regions.

Kinjo et al performed a prospective cohort study in 220,720 Japanese men and women, evaluating green tea and green-yellow vegetable consumption.[41] There was an increased risk of developing squamous cell cancer of the esophagus in individuals who drank scalding hot tea and ate only one to three servings of green-yellow vegetables per month.

In Shanghai, China, the incidence of squamous cell cancer of the esophagus has decreased while tobacco and alcohol intake has remained the same. Gao et al performed a population-based, case-control study to determine whether other risk factors could explain the decreasing incidence.[42] They reported that an increased consumption of fruits, vegetables, and meats providing increased dietary levels of protein, carotene, vitamins C and E, and riboflavin may be associated with a reduced risk of esophageal cancer. However, these researchers also documented a fivefold increase in risk among individuals consuming scalding hot soup or porridge.

Epidemiologic studies evaluating dietary habits also have been performed in the United States. N-nitroso compounds (along with nitrates, nitrites) found in preserved vegetables and salted foods in China and in processed meats, fish, and certain vegetables in the United States are carcinogenic in animals.[43]

A population-based, case-control study in western Washington state showed that consumption of nitrate-containing vegetables had a protective effect against the development of upper aerodigestive tract malignancies.[44] However, consumption of nitrate-containing meats was associated with an increased odds ratio of 1.82 (95% CI, 0.99 to 3.34) for developing squamous cell esophageal cancer. A similar study by Brown et al reported an increased risk of squamous cell cancer of the esophagus with a high intake of red meat and processed meat in both African-American and white males.[45]

### Adenocarcinoma

The relationship between dietary factors and esophageal adenocarcinoma is less clear. Dietary habits leading to obesity may have a role, specifically, diets low in fiber and vitamin C-rich fruits and vegetables and high in fat.[46,47] The prevalence of obesity is rising in the United States and in Europe. The association between obesity and esophageal adenocarcinoma is speculated to be due to increased GERD caused by increased abdominal girth and gastric pressure. Individuals with the highest decile of body mass have an odds ratio of 2.5 (95% CI, 1.2 to 5.0) for developing esophageal adenocarcinoma.[38,48]

Lagergren et al reported an even stronger association between obesity and esophageal adenocarcinoma in a population-based, case-control study in Sweden.[49] where incidence rates of esophageal adenocarcinoma are rising in proportions similar to those seen in the United States.[50] The study subjects were all white males and females born in Sweden. For individuals with a high body mass index (> 30 kg/m²), the odds ratio for developing adenocarcinoma was 16.2 (95% CI, 6.3 to 41.4), compared to those with the lowest body mass index (< 22 kg/m²). The reason for this strong association between obesity and esophageal adenocarcinoma is unclear.

#### Helicobacter pylori Infection

*Helicobacter pylori* infection, especially the cytotoxin-associated antigen (cagA)-positive strain, has been associated with gastric adenocarcinoma, noncardia type.[51,52] In contrast, Chow et al performed a multicenter case-control study showing an inverse relationship between *H pylori* infection and esophageal cancer in the United States.[53] The reduced risk of esophageal adenocarcinoma and gastric cardia adenocarcinoma associated with cagA-positive *H pylori* was unexpected.

The relationship between *H pylori* and GERD was evaluated by Vicari et al.[54] The prevalence of *H pylori* was approximately the same in patients with and without GERD. However, patients with severe GERD had a significantly lower prevalence of cagA-positive *H pylori* (P = .008). The presence of cagA-positive *H pylori* appears to protect against the development of esophageal
adenocarcinoma, perhaps because H pylori gastritis is associated with achlorhydria and a consequent decrease in acid production and reflux.

**Prevention of Esophageal Adenocarcinoma**

Significant controversies remain regarding the most appropriate clinical management of patients with Barrett’s esophagus. For more information, the reader is directed to guidelines recently published by Sampliner.\[55\]

Although multiple risk factors have been investigated, the most well-established association with esophageal adenocarcinoma is Barrett’s esophagus, a premalignant condition.\[5\] For this reason, prevention efforts for esophageal adenocarcinoma, both primary and secondary, have focused mainly on patients with this disease. Among Barrett’s patients, the incidence rate for glandular cancer is estimated to be 1% per year,\[9\] suggesting a window of opportunity for intervention in a substantial number of cases.

Currently, periodic performance of upper endoscopy to detect new-onset esophageal dysplasia is the most prevalent cancer prevention approach. Other potentially effective strategies include medical, surgical, or endoscopic therapy to inhibit, delay, or reverse malignant transformation in the columnar-lined esophagus.

**Screening and Surveillance**

Epidemiologic data demonstrate that white males ≥ 50 years old with long-standing symptoms of GER, comprise the population subgroup at greatest risk of developing Barrett’s esophagus.\[56\]

Screening endoscopy has been proposed for such persons,\[12,57\] but large, community-based programs have not been implemented because the associated merits and risks of this approach have not been rigorously evaluated. Surveillance endoscopy programs, however, are routinely employed for patients with known diagnoses of intestinal metaplasia. In support of this latter approach, uncontrolled studies have shown that esophageal cancer stage\[55,58\] and survival\[59,60\] may be favorably affected by surveillance.

The interval between endoscopic evaluations is typically determined by histologic findings, in accordance with recently published guidelines\[55\]: 2-3 years for two consecutive examinations in patients with no dysplasia, 6 months for incident and 12 months for those with stable low-grade dysplasia, and 3 months for those with confirmed high-grade dysplasia. (Alternatively, the last group may be referred for surgical resection.) Although widely adopted in clinical practice, this algorithm is based on observational data and expert opinion rather than randomized trial results. The full impact of these recommendations on the natural history of esophageal adenocarcinoma remains to be seen.

**Surgical Resection**

Extirpation of the target organ constitutes the most aggressive form of cancer prevention therapy for selected patients with Barrett’s esophagus. As noted above, this course of action is generally reserved for otherwise healthy individuals who are found to have high-grade dysplasia in one or more endoscopic biopsy specimens. The rationale for prophylactic esophagectomy is that undetected adenocarcinomas may be found in up to 73% of surgical specimens obtained in such cases.\[61-65\]

**Nonsurgical Approaches**

However, not all experts advocate immediate resection for noninvasive disease, chiefly because operative morbidity and mortality may be unacceptably high, particularly at centers in which experienced esophageal surgeons are not readily available. Preliminary data from 59 patients with high-grade dysplasia who were followed for 223 patient-years at the Hines Veterans Affairs Hospital support a nonsurgical approach to the management of Barrett’s esophagus.\[66\] Medical options include the use of histamine blockers or proton-pump inhibitors.

Alternatively, placement of a surgical fundoplication will prevent esophageal exposure to either acidic or alkaline refluxate. In addition to providing symptom relief, effective antacid therapy may promote at least partial reepithelialization of the distal esophagus with squamous mucosa\[67\] and may also lead to decreased cellular proliferation.\[68\]

Acid suppression has been coupled with various methods of mucosal ablation to evaluate the effects of combination therapy on dysplasia and superficial cancer. In a study by Overholt et al, omeprazole (Prilosec), 20 to 40 mg/d, coupled with an argon or potassium titanyl phosphate (KTP) laser and occasional neodymium:yttrium-aluminum-garnet (Nd:YAG) laser treatments resulted in histologic improvement in 13/14 (93%) patients with low-grade dysplasia, 64/73 (88%) with high-grade dysplasia, and 10/13 (77%) with adenocarcinoma (stages T1 or T2, N0, M0).\[69\] Similar results have been reported from smaller clinical studies of comparable design.\[70,71\]
Unfortunately, mucosal ablation may be associated with important complications, most prominently esophageal stricture but also including gastrointestinal bleeding, cardiac dysrythmias, and pleural effusions. Moreover, subsquamous foci of specialized columnar epithelium, dysplasia, and adenocarcinoma have been detected following therapy.[72,73] Further investigation of photoablation and thermal ablation in randomized, controlled trials is needed before these techniques can be routinely applied to esophageal adenocarcinoma prevention.

**Chemoprevention**

Cancer chemoprevention is defined as the use of pharmaceutical (or nutritional) agents to inhibit or reverse carcinogenesis prior to cellular invasion across the basement membrane. Relatively few chemopreventive agents have been tested against esophageal adenocarcinoma, but this is an area of active investigation.

**Nonsteroidal anti-inflammatory drugs (NSAIDs)** and their derivatives have generated substantial interest, due, in part, to reports of potential chemopreventive properties in multiple target organs, including the lung, breast, and gastrointestinal tract.[74] The antitumorigenic effects of NSAIDs are thought to involve inhibition of cyclooxygenase (particularly the cyclooxygenase-2 [COX-2] isoform) with downstream modulation of cancer-promoting prostaglandins.[75] In animal models, indomethacin has been shown to suppress upper gastrointestinal tract neoplasms.[76-78] Conversely, sulindac administration to carcinogen-induced rats has not yielded this same chemopreventive benefit.[79]

Epidemiologic data provide relatively strong support for NSAID chemoprevention of esophageal adenocarcinoma. Thun et al reported a 41% reduction in esophageal cancer mortality among regular aspirin users in the large American Cancer Society cohort, although this finding was not statistically significant (adjusted relative risk, 0.59; 95% CI, 0.34 to 1.03).[80] Funkhouser and Sharp noted a striking 90% reduction in esophageal cancer incidence among occasional aspirin users in the National Health and Nutrition Examination Survey and the National Epidemiologic Follow-up Studies (rate ratio, 0.10; 95% CI, 0.01 to 0.76).[81] Farrow and colleagues distinguished between histologic subtypes of esophageal cancer in their well-designed, case-control study, and observed significantly lower adjusted odds ratios for esophageal adenocarcinoma among aspirin users (odds ratio, 0.37; 95% CI, 0.24 to 0.58) and nonaspirin NSAID users (odds ratio, 0.57; 95% CI, 0.32 to 1.02).[82]

A new class of compounds, the selective COX-2 inhibitors, may afford the best efficacy:toxicity ratio. These agents are presently being evaluated in controlled intervention trials.

**Other compounds** of interest for esophageal adenocarcinoma chemoprevention include selenium, alpha-di-uoromethylornithine (DFMO), and retinoids. Selenium is an essential nonmetallic trace element involved in the function of critical cellular enzymes, such as glutathione peroxidase. Preclinical studies suggest that selenium may function as a chemopreventive through antioxidative, apoptotic, or other, as yet undefined, mechanisms. In the United States Nutritional Prevention of Cancer Study, treatment with 200 mg/d of high-selenium yeast for a mean of 4.5 years resulted in reduced esophageal cancer incidence, although too few cases were observed to allow for stratification by histologic subtype or for determination of precise risk estimates (relative risk, 0.33; 95% CI, 0.03 to 1.84).[83]

Alpha-difluoromethylornithine is an inhibitor of ornithine decarboxylase, an enzyme shown to have higher activity in Barrett’s mucosa relative to other upper gastrointestinal tissues.[84] Administration of DFMO can result in a decreased incidence of esophageal tumors in rodents[85] and modulation of potentially relevant biochemical pathways in human esophageal biopsy samples.[86] However, additional clinical data related to esophageal adenocarcinoma prevention are not yet available.

Retinoids putatively affect cellular proliferation through a nuclear receptor-mediated mechanism and perhaps also through altered arachidonic acid metabolism.[87] These compounds reportedly reduce the risk of several premalignant aerodigestive tract lesions, including oral leukoplakia, laryngeal papillomatosis, and bronchial metaplasia.[88] However, mixed results have been observed in Chinese esophageal cancer prevention trials, albeit using retinoids in combination with other agents and measuring end points associated with squamous cell carcinoma rather than adenocarcinoma.[89-92] The enthusiasm for retinoid chemoprevention is further tempered by the problematic toxicities of some of these compounds.[93] Newer synthetic retinoids may have improved safety profiles and could be considered for future esophageal cancer chemoprevention research.

**Summary**
Multiple risk factors for developing esophageal adenocarcinoma have been identified. These include medical conditions, such as Barrett’s esophagus, acid peptic disorders, motor disorders of the esophagus, and other malignancies; use of various medications; tobacco and alcohol consumption; diet and nutrition; and infection, particularly with H pylori. However, no one risk factor is responsible for the rising incidence of esophageal cancer. As we gain more insight into the biology of this disease, other risk factors hopefully will be identified that may enable us to decrease, stop, or even prevent the rising incidence of esophageal adenocarcinoma.

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